学位の種類	博士（医学）
報告番号	甲第１７７８号
学位記番号	第１２５７号
氏名	田中　達之
授与年月日	令和２年 ９月 25 日
学位論文の題名	Clinical and genetic investigation of 136 Japanese patients with congenital hypothyroidism. （先天性甲状腺機能低下症の日本人 136 人における臨床的・遺伝学的研究） Journal of Pediatric Endocrinology and Metabolism. 2020;33(6):691-701.
論文審査担当者	主査：　片岡 洋望

Abstract

Congenital hypothyroidism (CH) is the most common and heterogeneous disorder characterized by primary thyroid hormone deficiency caused by dyshormonogenesis or thyroid dysgenesis. Approximately 80–85% of cases are thought to be caused by thyroid dysgenesis (Szinnai, G. 2014. Clinical genetics of congenital hypothyroidism. *Endocrine Development*, *26*, 60–78.).Recent advances in genetic testing have revealed its causative mutations in some CH patients. In Japanese patients, the genetic abnormality detection rate in permanent CH and impaired hormone synthesis is around 20% (Mass Screening Committee, Japanese Society for Pediatric Endocrinology, Japanese Society for Mass Screening, Nagasaki, K., et al. (2015). Guidelines for Mass Screening of Congenital Hypothyroidism (2014 revision). *Clinical Pediatric Endocrinology : Case Reports and Clinical Investigations : Official Journal of the Japanese Society for Pediatric Endocrinology*, *24*(3), 107–133.). However, the underlying etiology remains unknown in most patients. This study aimed to perform clinical and genetic investigation in Japanese CH patients to uncover genotype-phenotype correlations. We enrolled 136 Japanese patients with transient or permanent CH between April 2015 and March 2017, and performed next-generation sequencing of 19 genes implicated in CH. We identified potentially pathogenic bi-allelic variants in DUOX2, TSHR, and TPO in 19, 5, and 1 patient, respectively (autosomal recessive), and a potentially pathogenic mono-allelic variant in NKX2-1 (autosomal dominant) in 1 patient. Molecular genetic diagnosis was highly suggested in 26 patients (19%) from 23 families. We also detected a potentially pathogenic mono-allelic variant in five recessive genes (DUOX2, TSHR, TG, DUOXA2, and TPO) in 31 unrelated patients (23%), although the patho- genicity of these variants remains inconclusive. Patients with bi-allelic DUOX2 variants showed a more severe clinical presentation in infancy than those with bi-allelic TSHR variants. However, this trend reversed beyond in-fancy. There were no statistical differences in initial thyroid stimulating hormone, free thyroxine, thyroglobulin, and levothyroxine dose as of March 2017 between patients with bi-allelic and mono-allelic DUOX2 variants. The prevalence of potentially pathogenic variants in Japanese CH patients was similar to that found by previous reports. Our study demonstrates a genotype- phenotype correlation in Japanese CH patients.